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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/096,247	06/11/98	DEFELIPPIS M	X-10675

HM22/0406

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EXAMINER	
RUSSEL, J	

ART UNIT	PAPER NUMBER
1654	6

DATE MAILED: 04/06/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/096,247	M. De Felippis et al
Examiner	**Group Art Unit**
J. Russel	1654

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to ~~communication(s)~~ application filed on 6-11-1998.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 1 - 16 is/are pending in the application.

Of the above claim(s)____ is/are withdrawn from consideration.

☐ Claim(s)____ is/are allowed.

☒ Claim(s) 1, 3, and 7-16 is/are rejected.

☒ Claim(s) 2 and 4-6 is/are objected to.

☐ Claim(s)____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4, 5

☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other____

Office Action Summary

1. Claims 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. At claim 8, line 1, "insulin analog" should be deleted, consistent with the preambles of the other claims. At claim 9, line 2, and claim 10, line 2, "monomeric" should be inserted before "insulin" so that there is direct antecedent basis in the claims for the phrase "the monomeric insulin analog".

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 7, and 11-14 are rejected under 35 U.S.C. 103(a) as being obvious over Bakaysa et al in view of Massey et al. Bakaysa et al teach stable and fast-acting monomeric insulin solutions comprising a buffer such as TRIS, zinc, a phenolic preservative such as m-cresol and phenol and mixtures thereof, and an isotonicity agent such as glycerin. The solution pH is about 7.4 to 7.5. The isotonicity agent concentration is preferably about 16 mg/ml. The solutions are used for parenteral administration of insulin. See, e.g., column 3, lines 1-17, and column 3, line 47 - column 5, line 13. Bakaysa et al do not teach the use of a TRIS buffer. Massey et al disclose that buffers such as TRIS are useful in retarding insulin aggregation and precipitation caused by pH drift. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use a TRIS buffer in the compositions of Bakaysa et al because TRIS is specifically named as a useful buffer for the compositions of Bakaysa et al and because Massey et al teach that TRIS buffers would be useful in preventing the aggregation and precipitation of insulin, a goal also desired by Bakaysa et al.

4. Claims 1, 3, 7, 8, and 10-16 are rejected under 35 U.S.C. 103(a) as being obvious over De Felippis '031 in view of Massey et al. De Felippis '031 teaches stable and fast-acting monomeric insulin solutions comprising a buffer such as TRIS, zinc, a phenolic preservative such as m-cresol and phenol and mixtures thereof, an isotonicity agent such as glycerin, and protamine. The monomeric insulin analog can be Asp^{B28}-human insulin. The solution pH is about 7.1 to 7.6, and

insulin concentrations can be 200U/ml. The isotonicity agent concentration is preferably about 16 mg/ml. The solutions are used for infusion of insulin. See, e.g., column 3, lines 1-4 and 22-25, and column 3, line 66 - column 4, line 66. De Felippis does not teach the use of a TRIS buffer. Massey et al disclose that buffers such as TRIS are useful in retarding insulin aggregation and precipitation caused by pH drift. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use a TRIS buffer in the compositions of De Felippis because TRIS is specifically named as a useful buffer for the compositions of De Felippis and because Massey et al teach that TRIS buffers would be useful in preventing the aggregation and precipitation of insulin, a goal also desired by De Felippis.

5. Claims 1, 7, and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Brange et al (U.S. Patent No. 4,472,385). Brange et al teach stable monocomponent insulin solutions comprising TRIS buffer, zinc, a phenolic preservative such as phenol, and an isotonicity agent such as glycerol. The solutions are used for continuous delivery of insulin. See, e.g., column 3, lines 58-60, and column 4, line 65 - column 6, line 11.

6. Claims 1, 7, and 11-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Brange et al (U.S. Patent No. 4,476,118). Brange et al teach stable monocomponent insulin solutions comprising TRIS buffer, zinc, a phenolic preservative such as phenol, and an isotonicity agent such as glycerol. The solutions are used for continuous delivery of insulin. See, e.g., column 6, lines 19-21, and column 8, lines 21-35.

7. Claims 2 and 4-6 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 9 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112 set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. The prior art of record does not teach the combination of $Lys^{B28}Pro^{B29}$-human insulin, Tris, zinc, and a phenolic preservative.

Bakaysa et al is not deemed to teach the use of a TRIS buffer because Bakaysa et al list only sodium phosphate as a preferred buffer (see column 4, lines 24-26); because the only exemplified buffer in Bakaysa et al is sodium phosphate (see Preparation 1 and Examples 1-2); and because the only specifically claimed buffer is sodium phosphate (see claim 5). Applicants' Tables 1 and 2 are deemed to set forth a probative side-by-side showing of an unexpected ability to prevent turbidity resulting from the use of TRIS buffer with $Lys^{B28}Pro^{B29}$-human insulin. Therefore to the extent that Bakaysa et al establish prima facie obviousness of the combination of TRIS buffer with $Lys^{B28}Pro^{B29}$-human insulin, this prima facie case is deemed to be rebutted by the showing of unexpected results set forth in the specification. However, Bakaysa et al teach all monomeric insulin analogs, not just $Lys^{B28}Pro^{B29}$-human insulin, and a showing of unexpected results for a single monomeric insulin analog is not deemed to be commensurate in scope with the generic claims rejected over Bakaysa et al in view of Massey et al as set forth above. If Applicants can provide similar evidence of unexpected results for another monomeric insulin analog, e.g., for Asp^{B28}-human insulin, then the examiner would find that the showing for the two

species of monomeric insulin analog is sufficient to support a conclusion of unexpected results for the entire genus of monomeric insulin analogs, and the rejection over Bakaysa et al in view of Massey et al set forth above would be withdrawn. For analogous reasons, a showing of unexpected results for two species of monomeric insulin analog would also overcome the rejection over De Felippis '031 in view of Massey et al set forth above.

Thurow is cited as art of interest. See Example 8. However, the examiner can find no evidence that De-B1-phenylalanine-insulin is a monomeric insulin analog, and its modification is remote from the positions on the B-chain which are modified in Applicants' exemplified monomeric insulin analogs (see page 8, lines 5-10). Accordingly, Thurow is not deemed to teach or suggest Applicants' claimed formulations.

It should be noted that the independent claims, limited to arginine as a buffer, would also be allowable over the prior art of record or any combination thereof. The prior art of record does not teach or suggest using arginine as a buffer for insulin formulations additionally comprising zinc and a phenolic preservative.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Cecilia Tsang can be reached at (703) 308-0254. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 305-7939 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.

Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

April 2, 1999